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Toxicity Report Series
Number 19

NTP Technical Report on Toxicity Studies of

Formic Acid

(CAS No: 64-18-6)

Administered by Inhalation to F344/N Rats and B6C3F$_1$ Mice

Morrow Thompson, DVM, PhD, Study Scientist
National Toxicology Program
Post Office Box 12233
Research Triangle Park, NC 27709

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CONTRIBUTORS

The NTP report on the toxicity studies of formic acid is based primarily on the 2-week studies that began in August, 1987, and ended in September, 1987, and the 13-week studies that began in December, 1987, and ended in March, 1988, at Battelle Northwest Laboratories.

National Toxicology Program
Evaluated experiment, interpreted results, and reported findings

Morrow Thompson, DVM, PhD
Study Scientist
John R. Bucher, PhD
Leo T. Burka, PhD
Rajendra S. Chhabra, PhD
Michael P. Dieter, PhD
Michael R. Elwell, DVM, PhD
Joel F. Mahler, DVM
H.B. Matthews, PhD
Errol Zeiger, PhD

Coordinated report preparation

Jane M. Lambert, BS
Kristine Witt, MS
Oak Ridge Associated Universities

Battelle Northwest Laboratories, Richland, WA
Principal contributors

B.J. Chou, DVM, PhD
Principal Investigator
J.R. Decker, BS
Bioengineer
J.A. Dill, PhD
Chemistry
C.L. Leach, PhD
Toxicologist
P.W. Mellick, DVM, PhD
Pathology
R.A. Miller, DVM, PhD
Pathology
H.A. Ragan, DVM
Clinical Pathology
S.E. Rowe, DVM, MS
Study Veterinarian
R.A. Renne, DVM
Pathology
R.B. Westerberg, PhD
Chemistry

NTP Pathology Working Group
Evaluated slides and prepared pathology report

John Seely, DVM
Chairperson
Pathco, Inc.
Michael R. Elwell, DVM, PhD
National Toxicology Program
Jerry Hardisty, DVM
Experimental Pathology Laboratories, Inc.
Michael Jokinen, DVM
National Toxicology Program
Joel Leininger, DVM, PhD
National Toxicology Program
William MacKenzie, DVM, MS
Experimental Pathology Laboratories, Inc.

Experimental Pathology Laboratories, Inc.
Provided pathology quality assessment

Jerry Hardisty, DVM
William MacKenzie, DVM, MS

Environmental Health Research and Testing, Inc.
Sperm morphology and vaginal cytology evaluation

Dushant K. Gulati, PhD
Teresa Cocanougher, BA
Susan Russell, BA

Analytical Sciences, Inc.
Statistical analysis

Richard Morris, MS
Steven Seilkop, MS
Janet Teague, MS

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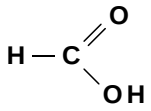

Molecular Formula: HCOOH
CAS No.: 64-18-6
Molecular Weight: 46

Synonyms: Aminic Acid, Formylic Acid, Methanoic Acid, Hydrogen Carboxylic Acid

ABSTRACT

Formic acid occurs in a variety of plants and fruits, mammalian tissues, and insect venoms. It is used industrially in preparing a variety of drugs, dyes, and chemicals; as a decalcifier; and in leather tanning. Formic acid also is an environmental contaminant of air and water and has been identified as the toxic intermediate (formate) in methanol poisoning. Two- and 13-week toxicity studies of formic acid were conducted in male and female F344/N rats and B6C3F_1 mice by whole body inhalation exposure to formic acid vapors. In addition, *in vitro* genetic toxicity studies were performed with *Salmonella typhimurium,* with or without metabolic activation. Formic acid was not mutagenic in this assay.

In 2-week studies, groups of 5 F344/N rats and 5 B6C3F_1 mice of each sex were exposed to formic acid for 6 hours a day, 5 days a week, at concentrations of 0, 31, 62.5, 125, 250, or 500 ppm. Deaths occurred in animals exposed to 500 ppm (rats and mice) and 250 ppm (1 female mouse). Microscopic lesions in the respiratory and olfactory epithelia occurred in rats and mice exposed to 62.5 ppm and higher concentrations, with the severity related to the exposure concentration. The lesions consisted of squamous metaplasia, necrosis, and inflammation. Exposures had minimal or no effects on coagulation times, blood pH and electrolytes, or on concentrations and activities of urine analytes in rats during the 2-week studies.

In 13-week studies, groups of 10 animals of each species and sex were exposed to formic acid at concentrations of 0, 8, 16, 32, 64, and 128 ppm for 6 hours a day, 5 days a week. Two mice, 1 male and 1 female, died in the 128 ppm groups. Body weight gains were significantly decreased in mice exposed to 64 and 128 ppm formic acid. Microscopic changes in rats and mice ranged from minimal to mild in severity and generally were limited to animals in the 128 ppm groups. Lesions related to exposure to formic acid consisted of squamous metaplasia and degeneration

of the respiratory and olfactory epithelia, respectively. Hematologic and serum biochemical changes at interim and terminal time points were minimal to mild and, generally, were consistent with hemoconcentration.

Overall, the effects of formic acid were consistent with those of irritant chemicals administered by inhalation exposure. The no-observed-adverse-effect level (NOAEL) for respiratory injury was 32 ppm in rats and mice. There was no significant evidence of systemic toxicity in these studies.

PEER REVIEW

Peer Review Panel

The members of the Peer Review Panel who evaluated the draft report on the toxicity studies on formic acid on July 10, 1991, are listed below. Panel members serve as independent scientists, not as representatives of any institution, company, or governmental agency. In this capacity, panel members act to determine if the design and conditions of the NTP studies were appropriate and to ensure that the toxicity study report fully and clearly presents the experimental results and conclusions.

National Toxicology Program's Board of Scientific Counselors Technical Reports Review Subcommittee

Paul T. Bailey, PhD
Mobil Oil Corporation
Toxicology Division
Princeton, NJ

Louis S. Beliczky, MS, MPH
Director of Industrial Hygiene
Department of Industrial Hygiene
United Rubber Workers Intl. Union
87 South High Street
Akron, OH

Gary P. Carlson, PhD
Department of Pharmacology and Toxicology
Purdue University
West Lafayette, IN

Harold Davis, DVM, PhD
School of Aerospace Medicine
Brooks Air Force Base, TX

Robert H. Garman, DVM
Consultants in Veterinary Pathology
Murrysville, PA

Jay I. Goodman, PhD
Department of Pharmacology and Toxicology
Michigan State University
East Lansing, MI

David W. Hayden, DVM, PhD
Department of Veterinary Pathobiology
College of Veterinary Medicine
University of Minnesota
St. Paul, MN

Curtis D. Klaassen, PhD
Department of Pharmacology and Toxicology
University of Kansas Medical Center
Kansas City, KS

Daniel S. Longnecker, MD
Department of Pathology
Dartmouth Medical School
Hanover, NH

Barbara McKnight, PhD
Department of Biostatistics
University of Washington
Seattle, WA

Ellen K. Silbergeld, PhD*
University of Maryland Medical School
Baltimore, MD

Lauren Zeise, PhD
California Department of Health Services
Berkeley, CA

*unable to attend

Summary of Peer Review Comments

On July 9 and 10, 1991, the Technical Reports Review Subcommittee of the Board of Scientific Counselors for the National Toxicology Program met in Research Triangle Park, NC, to review the draft technical report on toxicity studies of formic acid

Dr. M. Thompson, NIEHS, introduced the short-term toxicity study report by reviewing the natural occurrences and uses of formic acid, the experimental design, and the results.

Dr. Carlson, a principal reviewer, said the study was well done. He asked at what point after the 2-week study the blood pH was determined, noting that adidosis is an important problem with the acute toxicity of methanol through its metabolism to formate. Dr. Thompson said pH was determined the day following the last exposure to formic acid. Dr. Carlson also asked that a rationale be given for administering the chemical by inhalation. Dr. Thompson said that formic acid had been nominated for study because of its structural relationship with formaldehyde and because inhalation is an important route of exposure for humans.

Dr. Klaassen, a second principal reviewer, said the study was performed well. He said he was concerned that the report may over-emphasize that rodent data on formic acid exposure may not be applicable to humans. He said the localized toxic effects observed might be very relevant for humans. Dr. Thompson said the lack of a systemic toxic effect in rats may be related to their resistance to formate toxicity, and that this was the reason for the emphasis. Dr. Klaassen agreed but said that the possible similarity in local toxic effects among rodents and humans should be made more clear.

Dr. Zeise questioned the NOAEL reported in the study (32 ppm), noting a reported olfactory epithelial lesion in a male rat at 32 ppm in the 13-week study. Dr. M. Elwell, NIEHS, said the olfactory degeneration was a minimal change and that it was difficult to cite it as a treatment effect.

After discussion of editorial matters, the panel agreed to accept to report, with the suggested changes.